REMARKS

Claims 3, 4, 14, 15, 18-22, 29, 30, 34, 40, and 51-76 are pending. Claims 3, 51-53, and 55-75 are amended. The claim amendments to claims 3 and 53 are supported by the specification, for example, at paragraph [0076]. The amendments to claims 51, 52, and 55-75 are of a formal nature and are made to improve the form of the claims. New claim 76 is supported by the specification, for example, at paragraph [0076].

35 U.S.C. 102 Rejection

Reconsideration is respectfully requested of the rejection of claims 3, 4, 14, 15, 18, 19, 21, 29, and 51-75 as anticipated by Gardon et al. (U.S. Patent No. 3,874,907) under 35 U.S.C. § 102(b).

Claim 3

Claim 3 is directed to an oral or rectal pharmaceutical composition comprising a pharmaceutically acceptable excipient and core-shell particles. These core-shell particles comprise a core component and a shell component; the core component comprises a potassium-binding cation exchange polymer and the shell component comprises a crosslinked polymer having a permeability for potassium ion that is higher than the permeability for a competing cation, and having a thickness ranging from about 0.002 microns to about 50 microns. The shell component is essentially not disintegrated during residence and passage through the gastro-intestinal tract of an animal subject.

Gardon et al. disclose microparticles for use in separating urea from saline solutions in artificial dialysis machines or ultrafiltration kidney machines. These microparticles have a core of crosslinked polymer with sulphonic acid groups and a polymer skin coating that contains quaternary ammonium groups.

Gardon et al. do not disclose the oral or rectal pharmaceutical compositions of claim 3. Gardon et al. merely disclose microparticles that are used in kidney or dialysis machines; they are not administered orally or rectally to a patient and do not contact the gastrointestinal tract as required by claim 3. Thus, Gardon et al. do not disclose an oral or rectal pharmaceutical composition as required by claim 3.

Further, contrary to the Office's assertion that the "microparticles would inherently pass through the intestine without disintegrating,"[1] the Gardon particles would not have necessarily had this property.

As noted in M.P.E.P. §2112.IV, a rejection based upon the inherency of a claimed element must be supported by evidence that the missing element is necessarily present in the reference:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). . . .
>
> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original) (Applicant's invention was directed to a biaxially oriented, flexible dilation catheter balloon (a tube which expands upon inflation) used, for example, in clearing the blood vessels of heart patients). The examiner applied a U.S. patent to Schjeldahl which disclosed injection molding a tubular preform and then injecting air into the preform to expand it against a mold (blow molding). The reference did not directly state that the end product balloon was biaxially oriented. It did disclose that the balloon was "formed from a thin flexible inelastic, high tensile strength, biaxially oriented synthetic plastic material." *Id.* at 1462 (emphasis in original). The examiner argued that Schjeldahl's balloon was inherently biaxially oriented. The Board reversed on the basis that the examiner did not provide objective evidence or cogent technical reasoning to support the conclusion of inherency.).

---

[1] See Office action dated July 14, 2008 at page 3.

Applicants respectfully submit that the present rejection is not supported by objective evidence or cogent technical reasoning to support the conclusion of inherency with regard to the disintegration of the shell in the gastrointestinal tract. There is no reason given by the Office why the shell components of Gardon would not have disintegrated in the gastrointestinal tract as required by claim 3. Since the Gardon reference does not disclose contact of the particles with the gastrointestinal tract, the lack of disintegration of the shell components upon residence and passage through the gastrointestinal tract would *not* have necessarily and inevitably been present in the Gardon particles. The examiner has not provided a reasonable basis to conclude that any of the Gardon particles would necessarily transit the gastrointestinal tract without disintegration of the shell component. Even if the broad disclosure of Gardon describes particles that have similar composition to the claimed particles, the Gardon reference does not contemplate administration of the particles so they transit the gastrointestinal tract and this generic disclosure is not sufficient for Gardon to anticipate claim 3. In *Metabolite Labs, Inc. v Lab. Corp. of Am Holdings*, the Federal Circuit stated that a "prior art reference that discloses a genus still does not inherently disclose all species within that broad category."[2] Thus, Gardon may disclose a genus that encompasses the claimed particles, but particles having a shell component that does not disintegrate upon transit through the gastrointestinal tract is not inherently disclosed by Gardon et al.

Additionally, the M.P.E.P. indicates that "clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention...."[3] Applicant's reliance on the preamble "oral or rectal pharmaceutical" and the element of the shell component not disintegrating upon transit through the gastrointestinal tract to distinguish the Gardon particles transforms the preamble and the elements into claim limitations that cannot be disregarded in determining patentability.

---

[2] *Metabolite Labs, Inc. v Lab. Corp. of Am Holdings*, 370 F.3d 1354, 1367, 71 U.S.P.Q.2d 1081, 1091 (Fed. Cir. 2004).

[3] M.P.E.P. § 2111.02; *Catalina Mktg. Int'l v Coolsavings.com, Inc.*, 289 F.3d at 808-809, 62 U.S.P.Q.2d, 1781, 1785 (Fed. Cir. 2002).

Claim 53

Claim 53 is directed to an oral pharmaceutical composition comprising a pharmaceutically acceptable excipient and core-shell particles. These core-shell particles comprise a core component and a shell component. The core component comprises a potassium-binding cation exchange polymer. The shell component comprises a crosslinked polymer having a permeability for potassium ion that is higher than the permeability for a competing cation, the weight ratio of the shell component polymer to the core component polymer ranging from about 0.0001:1 to about 0.5:1. The shell component is essentially not disintegrated during residence and passage through the gastro-intestinal tract of an animal subject. Claim 53 is not anticipated by Gardon et al. for at least the same reasons as claim 3.

In summary, claims 4, 14, 15, 18, 19, 21, 29, 51, 52, and 54-76 depend directly or indirectly from claim 3 or claim 53, incorporate all the elements of claim 3 or claim 53, and accordingly, are not anticipated for the same reasons as claim 3 and claim 53. Therefore, claims 3, 4, 14, 15, 18, 19, 21, 29, and 51-76 are not anticipated by Gardon et al. (U.S. Patent No. 3,874,907) under 35 U.S.C. § 102(b).

35 U.S.C. 103 Rejection

Reconsideration is respectfully requested of the rejection of claims 3, 4, 14, 15, 18, 19, 21, 29, 30, 34, 40, and 51-75 as unpatentable over Kamakura et al. (U.S. Patent No. 6,280,717), in view of Gardon et al. (U.S. Patent No. 3,874,907) and Heese et al. (U.S. Application Publication No. 2002/0054913) under 35 U.S.C. § 103(a).

Kamakura et al. describe cation exchange resin preparations having a resin and a gelling agent and can further include a binder. The preparation is intended to decrease the sandy feel in the mouth and throat that a patient taking a cation exchange resin typically experiences. Further, after granulation of the resin and a gelling agent, the particles of the preparation can be coated with a sweetener and methylcellulose. Heese et al. describes particles having an enteric coating.

The Office asserts that it would have been obvious to combine the Gardon particles into the pharmaceutical formulation of the Kamakura patent with "an expected result of a stable formulation useful in treating renal disorders" since they both comprise sulphonated core

particles useful in cation exchange.[4] The Office further asserts that Heese et al. "would provide the enteric coating to the core-shell polymers improving the stability of the particles and provide proper administration of the particles in the appropriate portion of the intestine."[5]

However, Applicants respectfully assert that a person of ordinary skill would not have had a reasonable expectation that the combination of the Kamakura and Gardon disclosures would have provided a beneficial therapeutic agent due to the unpredictability of the suitability of the Gardon particles for oral or rectal administration to animals and the lack of guidance regarding such a combination. Further, the Office has provided no technical reason why a skilled person would have selected the combination of Gardon and Kamakura particles from the universe of sulphonated cation exchange polymers without using Applicant's claims as a template.

The Kamakura particles are not core-shell particles as claimed because they do not include a crosslinked polymer as required by claims 3 and 53. While the Office asserts that the sweetener and methylcellulose coating of Kamakura can be considered a shell polymer, methylcellulose is not a crosslinked polymer produced by free radical polymerization of an ethylenic monomer. Further, a crosslinked polymer provides advantageous mechanical properties to the shell that are lacking in the uncrosslinked methylcellulose coating of Kamakura that is intended to make the oral formulation more palatable and to dissolve once the particles are combined with water upon administration to a patient.

As noted above, Gardon et al. do not disclose oral or rectal pharmaceutical compositions and one of ordinary skill would not have considered Gardon et al. in formulating the oral formulation of Kamakura. Gardon et al. do not disclose administering their microparticles to an animal. They merely use them in kidney or dialysis machines where certain microcapsules are used to remove "undesirable products, such as urea."[6] Furthermore, "these microcapsules possess a high urea/salt selectivity, that is to say that they retain urea whilst *being rather impermeable to* ***salt***."[7] In view of the fact that Gardon et al. does not disclose exposing particles to the gastrointestinal tract, and in particular, since potassium ions are more available in the

---

[4] See Office action dated July 14, 2008 at pages 7-8, paragraph 10.

[5] See id.

[6] Gardon et al. (U.S. Patent No. 3,874,907) at column 2, lines 9-18 and column 14, lines 12-15.

[7] Id. at column 14, lines 16-18, emphasis added.

colon than in the small intestine, Gardon et al. do not disclose nor provide a reasonable expectation of success of their particles allowing for a core to bind and hold potassium for passage out of the gastrointestinal tract. The "reasonable expectation of success" does not reach that far, as the Federal Circuit stated in *Eisai Co. v. Dr. Reddy's Laboratories, Inc.*[8] :

> First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. See Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007). ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."). Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable. (Emphasis added)

If anything, Gardon et al. would have provided a reason for a skilled person not to expect that the Gardon particles would have been effective at binding potassium. The impermeability to salt of the shell polymers, as described by Gardon, would have also led a skilled person away from the claimed invention because of the relative unavailability of potassium ion to the polystyrene sulfonate core material of Kamakura and caused a skilled person to doubt the efficacy of the Gardon et al. particles for potassium binding.

Moreover, given Gardon et al.'s tangential relationship to the claimed invention, one skilled in the art would not have selected Gardon et al. from the vast number of sulphonated cation exchange polymer references because the skilled person would have had no reason to look to this dialysis art for removing urea in formulating an oral or rectal composition, absent the applicants claims as a template for hindsight reconstruction of claims 3 and 53. Gardon et al. is

[8] *Eisai Co. v. Dr. Reddy's Laboratories, Inc.*, 87 U.S.P.Q.2d 1452 (Fed. Cir. 2008).

not one of a small and finite number of alternatives known in the art. Instead a vast universe of sulfonated cation exchange polymers were known in the art and the Office has failed to provide a reason that a person of ordinary skill would have selected the polymers of Gardon et al. in formulating an oral or rectal pharmaceutical composition as claimed. Applicants respectfully submit that without showing a reason for the selection, a prima facie case of obviousness has not been established.

Moreover, Gardon does not remedy the deficiencies of Kamakura. While the Gardon reference does describe various crosslinked shell polymers, it does not provide any basis for a skilled person to have a reasonable expectation that a beneficial potassium binding effect would have been found when substituting the shell polymers of Gardon described for the purpose of selectively binding urea over salt for the methylcellulose and sweetener coating of the Kamakura composition used to improve the palatability of the polystyrene sulfonate. Given that there was no reason in the art for a skilled person to contemplate combining the teachings of Kamakura with those of Gardon and no reasonable expectation of success, claims 3 and 53 are patentable over these references.

Nor would the combination of Kamakura in view of Gardon and Heese have rendered claim 30 obvious. Heese is directed to pharmaceutical compositions having small molecule active agents and polymeric drug delivery systems. In some of the embodiments, the polymeric drug delivery systems could be considered an enteric coating. However, Heese does not remedy the deficiencies of Kamakura and Gardon. Heese would not have provided a reason why a skilled person would have had a reasonable expectation that an effective potassium binding oral or rectal pharmaceutical composition would have resulted from the combined teachings. Further, Heese would not have provided a reason for combining any of the cited references. While Heese does describe various polymers having cation exchange capability, this capability is used to absorb protons in the storage environment, and in turn, provide storage stable pharmaceutical compositions. There is no reason why a skilled person would have contemplated adding the enteric coating of Heese to the core shell particles of Kamakura and Gardon or would have expected it to provide beneficial potassium binding compositions.

Additionally, the Office asserts that the elements requiring potassium binding and the shell component not disintegrating upon transit through the gastrointestinal tract are inherently met by Gardon. However, the *Spormann* court stated that obviousness and inherency are

different questions and "[t]hat which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."[9] Thus, since it is unknown whether the Gardon particles would have the claimed elements, the claimed pharmaceutical compositions cannot be obvious from the Gardon disclosure.

In sum, claims 3, 53, and the claims that depend therefrom are patentable in view of the cited references.

Claims 34 and 40

Claim 34 is directed to a method of removing potassium in which a composition containing a core-shell particle is administered to an animal suffering from renal insufficiency, renal failure, end stage renal disease (ESRD) or combinations thereof. Claim 40 is directed to a method of removing potassium in which a composition containing a core-shell particle is administered to an animal suffering from hyperkalemia. From the teachings of Kamakura, Gardon, and Heese, a person of ordinary skill would not have had a reasonable expectation that such a method would have provided a therapeutic effect. These cited references are described in detail above. Kamakura et al. describe pharmaceutical compositions containing a polystyrene sulfonate resin combined with various gelling and/or binding agents that can have a sweetener/methylcellulose coating. The additives to the resin are used to improve the palatability of the resin and thus, to improve patient compliance. Additionally, Gardon et al. employ a microcapsule to remove ***urea***, ex vivo, a microcapsule that possesses a high urea/salt selectivity and *is rather impermeable to* ***salt***." If anything, Gardon et al. would have provided a reason for a skilled person not to expect that the Gardon particles would have been effective at binding potassium. The impermeability to salt of the shell polymers described by Gardon would have also led a skilled person to believe that the shells would be rather impermeable to potassium. This impermeability to potassium would have decreased the potassium binding ability of the polystyrene sulfonate core material of Kamakura and caused a skilled person to doubt the efficacy of the Gardon particles for potassium binding.

[9] *In re Spormann*, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966).

Moreover, the applied prior art must contain not only teachings to arrive at the claimed invention, but evidence indicating that it would be successful.[10] While Kamakura provides information regarding polystyrene sulphonate polymers as potassium binding polymers and Gardon describes particles used to remove urea in an ex vivo system, nothing in Gardon or Kamakura would have taught that the Gardon particles could be administered to a patient successfully to remove potassium. Kamakura and Gardon use different polymers. And, a skilled person would not have known whether the Gardon particles could have been safely administered to a patient. Further, as described above a skilled person would have believed that the Gardon particles would not bind enough potassium to provide a therapeutic effect as required by the claims.

Kamakura does not help. A person of ordinary skill would not have been led to administer Gardon et al.'s urea-binding/salt-impermeable microcapsules to an animal to bind potassium just because Kamakura used anion exchange resins having a palatable methylcellulose coating to remove potassium. Similarly, a person of ordinary skill would not have incorporated Gardon et al.'s ex vivo urea-binding/salt-impermeable microcapsules into a pharmaceutical composition to administer to a patient just because Kamakura used anion exchange resins to remove potassium. It is clear that Gardon et al. intended their microcapsules for ex vivo use and nothing in Kamakura et al. or Gardon et al. would have suggested in vivo administration of core-shell particles as described by claims 34 or 40. Thus, claims 34 and 40 are patentable in view of Kamakura et al. and Gardon et al.

And, Heese et al. does not cure the defects. The polymer-drug pharmaceutical complex described by Heese et al. had an enteric coating in some embodiments. This embodiment included a coating that prevented anions in the stomach and upper gastrointestinal tract from displacing the anionic drug from the anion exchange polymer before the coating was disintegrated. Once the complex reached the portion of the gastrointestinal tract where the enteric coating was disintegrated, anions could displace the anionic drug, which could in turn be absorbed into the system. Heese et al. thus use the polymer as a drug delivery system, and is otherwise inapplicable to the claimed invention. The Office's assertion is the product of impermissible hindsight reasoning using applicant's claims as a template. Thus, claims 34 and

[10] *In re Eli Lilly*, 902 F.2d 943, 945, 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990).

40 and the claims that depend therefrom are patentable in view of the cited references under 35 U.S.C. § 103(a).

In conclusion, claims 3, 34, 40, 53, and the claims that depend therefrom, are patentable in view of the cited references. Applicants respectfully request that this basis for rejection be withdrawn.

Provisional Double Patenting Rejection

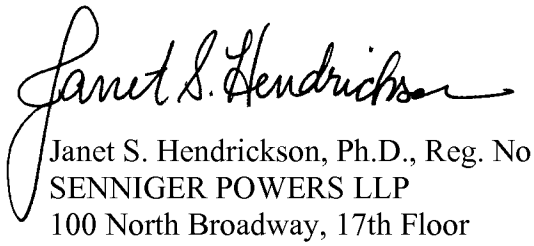
The Office provisionally rejects claims 3, 4, 14, 15, 18-22, 29, 30, 34, 36, 40, and 51-75 on the ground of nonstatutory obvious-type double patenting over claims 1, 10, 16, 17, 20-24, 31, 32, and 45-65 of copending U.S. Serial No. 10/813,872. Without conceding the propriety of this rejection, applicant will consider filing a terminal disclaimer to obviate this basis for rejection when the application is otherwise in condition for allowance.

CONCLUSION

Applicant submits that the present application is now in condition for allowance and requests early allowance of the pending claims.

The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,



Janet S. Hendrickson, Ph.D., Reg. No. 55,258
SENNIGER POWERS LLP
100 North Broadway, 17th Floor
St. Louis, Missouri 63102
(314) 231-5400

JSH/clp